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NARRATIVE LITERATURE REVIEW

Gaucher disease: a systemic and ophthalmological review

Doença de gaucher: revisão sistêmica e oftalmológica

Enfermedad de gaucher: revisión sistémica y oftalmológica

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ABSTRACT

Gaucher disease(GD) is autosomal recessive due to the deficiency of the acid beta glucosidase enzyme caused by mutations in the 1q21 gene, promoting the accumulation of glucosylceramide in cells of the reticuloendothelial system. The main clinical manifestations of the DG are anemia, thrombocytopenia, hepatosplenomegaly, bone alterations and neurological manifestations and they are related to macrophages loaded with non-metabolized fats. The main clinical presentations are non-neuronopathic (DG1), acute neuronopathic (DG2) and subacute neuronopathic (DG3). Other organs, such as the lungs, kidneys and eyes, may be affected. Significant ocular alterations and oculomotor disorders may occur in DG. The treatment of DG is clinical and must be carried out during the life. Although the success of treatment of ocular manifestations is still questionable, ophthalmologic assessment is of great importance for the follow-up of patients with DG.

Keywords: Gaucher Disease, Glucosylceramide, Macrophages.

RESUMO

A doença de Gaucher DG é autossômica recessiva decorrente da deficiência da enzima beta-glucosidase ácida causada por mutações no gene 1q21, promovendo o acúmulo de glucosilceramida na células do sistema reticuloendotelial. As principais manifestações clínicas da DG são anemia, trombocitopenia, hepatoesplenomegalia, alterações ósseas e manifestações neurológicas, que são relacionadas aos macrófagos carregados de gorduras não metabolizadas. As principais apresentações clínicas são doença não-neuronopática (DG1), neuronopática aguda (DG2) e neuronopática subaguda (DG3). Outros órgãos, como pulmões, rins e olhos, podem ser acometidos. Importantes alterações oculares e distúrbios oculomotores podem ocorrer na DG. O tratamento da DG é clínico e deve ser realizado por toda vida. Embora o sucesso do tratamento das manifestações oculares ainda seja questionável, a avaliação oftalmológica é de grande importância no seguimento dos pacientes com DG.

Palavras-chave: Doença de Gaucher, Glucosilceramida, Macrófagos.

RESUMEN

La enfermedad de Gaucher (EG) es autosómica recesiva consecuente de la deficiencia de la enzima beta-glucosidase ácida causada por mutaciones en el gene 1q21, promoviendo el acúmulo de glucosilceramida en la células del sistema reticuloendotelial. Las principales manifestaciones clínicas de la EG son anemia, trombocitopenia, hepatoesplenomegalia, alteraciones óseas y manifestaciones neurológicas, las cuales están relacionadas a los macrófagos cargados de grasas no metabolizadas. Las principales presentaciones clínicas son enfermedad no neuronopática (EG1), neuronopática aguda (EG2) y neuronopática subaguda (EG3). Otros órganos, como pulmones, riñones y ojos, pueden ser acometidos. Importantes alteraciones oculares y disturbios oculomotores pueden ocurrir en la EG. El tratamiento de la EG es clínico y debe realizarse de manera vitalicia. Aunque el éxito del tratamiento de las manifestaciones oculares aún sea cuestionable, la evaluación oftalmológica es de grande importancia en el seguimiento de los pacientes con EG.

Palabras Clave: Enfermedad de Gaucher; Glucosilceramida; Macrófagos.

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Gaucher disease (GD, OMIM #230800, ORPHA355) is a rare genetic disease caused by mutations in the GBA1 gene (GBA; 606463), which is located on chromosome 1 (1q21)[1], that sharply reduce the activity of the enzyme glucocerebrosidase (GCase, also known as glucosylceramidase or acid β-glucosidase, EC 4.2.1.25) in the lysosomes. GCase hydrolyzes glucosylceramide (GlcCer) into ceramide and glucose resulting from the degradation of red and white blood cell membranes. Its deficiency, therefore, leads to glucocerebroside accumulation in tissues, especially in mononuclear phagocyte system cells.[2]

EPIDEMIOLOGY

The available data on the birth incidence of GD in the general population in several countries ranges from 0.39 to 5.80 per 100,000 births, while the birth prevalence ranges from 1.33 to 1.75 per 100,000 births.[3] The autosomal recessive inheritance of GD allows the inference that consanguineous marriages and the founder effect of certain mutations in specific populations can lead to the phenotypic manifestations of recessive genes over several generations as verified in the town of Tabuleiro do Norte, State of Ceará, Brazil where the prevalence of the disease is approximately 1:4,000 people.[4]

CLINICAL MANIFESTATIONS

The clinical manifestations of GD are associated with different actions of the following two types of macrophages: M1 (classically activated macrophages) and M2 (alternatively activated macrophages). M2 macrophages are believed to be involved in the production of cytokines, chemokines, and other molecules including IL-1; IL-6; IL-8; TNF-α (tumor necrosis factor alpha); M-CSF (macrophage colony-stimulating factor); MIP-1; IL-18; IL-10; TGF; CCL- 18; chitotriosidase; and CD14s, being responsible for the disease's "pseudo-inflammatory" reactions[5-7]. Macrophages engorged with fat, characterized by fibrillar cytoplasm with a "crumpled paper" appearance and eccentric nuclei, reacting positively to PAS (periodic acid-Schiff) staining, are called "Gaucher cells" (GC).[8]

More than 300 mutations cause GD and, alone as well as in combination in both alleles, can determine the phenotypic manifestations: type 1 or non- neuronopathic (94%; GD1, OMIM #230800); type 2 or acute neuronopathic (GD2, OMIM #230900), or type 3, also called subacute neuronopathic (GD3, OMIM #231000).[9,10]

The rarity of the disease and the heterogeneous clinical manifestations hinder the early diagnosis of GD.[11] GD1 is characterized by hepatosplenomegaly, anemia with thrombocytopenia, lung diseases, presence of clinical or radiographic evidence of bone diseases, and absence of primary central nervous system diseases (Figure 1).[12]



Figure 1. Gaucher disease patient with marked hepatosplenomegaly and skeletal involvement observed on magnetic resonance imaging of the femora.

GD2 (<5% of cases) has its onset before age 2, with impaired psychomotor development and a fast, progressive course that leads to death between 2 and 4 years[12]. Patients experience severe neurological impairment, consisting of neck and trunk spasticity (opisthotonus), bulbar signs (especially severe swallowing disorders), and oculomotor nerve palsy (or bilateral strabismus fixus). In addition to these signs, there may also be trismus and hypertonia with pyramidal and possibly extrapyramidal rigidity[7].

The GD3 form, also called juvenile or subacute neurological GD, represents only 5% of GD cases, although it can reach up to 33% in some groups of patients[13]. These patients usually present with the visceral manifestations described in GD1 associated with oculomotor neurological involvement that appear in most cases before the age of 20 years. Some patients have moderate systemic involvement, with horizontal ophthalmoplegia as the only neurological symptom, while others feature more serious forms, with several neurological signs including progressive myoclonus epilepsy (16% of patients), cerebellar ataxia or spasticity (20%–50% of patients), and, in some cases, dementia[14,15].

OPHTHALMOLOGICAL MANIFESTATIONS

Ophthalmological changes in GD can manifest in the anterior and posterior segments in addition to affecting eye movements in some instances because of the neurological changes.[16-18]

CHANGES IN THE ANTERIOR SEGMENT OF THE EYE

Gaucher first described in 1882 a disease that caused enlarged spleen with jaundice and yellowish conjunctiva. According to McNee (1937), in this disease “the eyes show a phenomenon which is so constant as to be almost pathognomonic: a brownish-yellow wedge-shaped thickening or pinguecula appears first on the nasal and then on the temporal side of each eye”.[19] The biopsy of the pinguecula showed a degenerated, foamy cytoplasm with no fat particles, similar to that observed in spleen cells in GD cases.[19] Recent histopathological studies found pinguecula elastosis.[20]

The ocular manifestations of GD1 include white deposits scattered throughout the corneal endothelium, anterior chamber angle, ciliary body, and pupillary margin. Corneal involvement is variable and correlates with the type of mutation.[21] Bilateral corneal opacity has been observed on three levels using biomicroscopy. They featured evident scattered areas of subepithelial opacity and focal areas of thickening and opacities in the stroma which were greater in the posterior third. The architecture of the corneal stroma is distorted with keratocytes interspersed with multiple small white dots caused by extensive cytoplasmic vacuolation. The deep stroma has a spiculated appearance. Corneal opacities are presumed to result from the accumulation of GlcCer in the keratocytes. Endothelial cell count may be lower than that expected for the patient’s age.[22]

CHANGES IN THE POSTERIOR SEGMENT OF THE EYE

Fundus abnormalities include perimacular ring-shaped pigmented lesions, typical white retinal lesions that occur because of the preretinal accumulation of glycolipids, macular atrophy, retinal hemorrhages, and edema caused by increased retinal vascular permeability.[21,23]

Vitreous opacities are the most frequently occurring manifestations in patients with GD and they are present in 3% of cases[24]. This finding has been noted to be more frequent after splenectomy due to increased glucosylceramide circulation[25]. Takehisa *et al.* assessed sphingolipids in a patient with GD and detected ceramide monohexoside accumulation in the vitreous humor using chromatography[26].

Shrier *et al.* described a vascular tortuosity with a spiral pattern similar to that in Fabry disease as well as the presence of an epiretinal membrane. They also reported the presence of GC in the vitreous cavity, along with large quantities of GlcCer[25].

The pathophysiology of the GC in the retina remains unclear, but higher levels of circulating GlcCer in unusual systemic sites have been suggested as the cause for these changes. Retinal GlcCer deposition is an end product of the breakdown of myelin, white blood cells, red blood cells, and endothelial cells. The cells in the retina that absorb this substrate are glial cells: Müller cells, astroglia, and especially microglia.[27,28] However, it is not clearly understood whether GlcCer accumulation produces functional changes in the retina of patients who are still visually asymptomatic. Visual function impairment and progressive retinal involvement despite enzyme replacement therapy have been described[27].

Seidova *et al.* described preretinal lesions and subclinical abnormalities on the electroretinogram (ERG) which were attributed to the accumulation of storage lipids in glial cells.[27] An association between GD and retinitis pigmentosa has also been proposed since the liver disease leads to vitamin A deficiency.[29]

There are case reports of patients with GD3 presenting white peripapillary and perivascular deposits on the posterior pole of the eye, which are described in the optical coherence tomography (OCT) as hyporeflective preretinal lesions in the vitreoretinal interface associated with localized posterior vitreous detachment (Figure 2)[30,31].

Wang *et al.* also described yellow-white macular lesions in both eyes. Fluorescein angiography evidenced changes in the retinal pigment epithelium of the right eye macula and irregular areas of hyperfluorescence in the left one.

The retinal vessels showed contrast extravasation, especially in the peripapillary region.[21]

Central retinal artery branch occlusion has been described in a patient with complicated GD, raising the hypothesis that microthrombi are a part of the etiology of the obstruction of this vessel[32]. Tractional retinal detachment has also been reported in patients with GD[33].

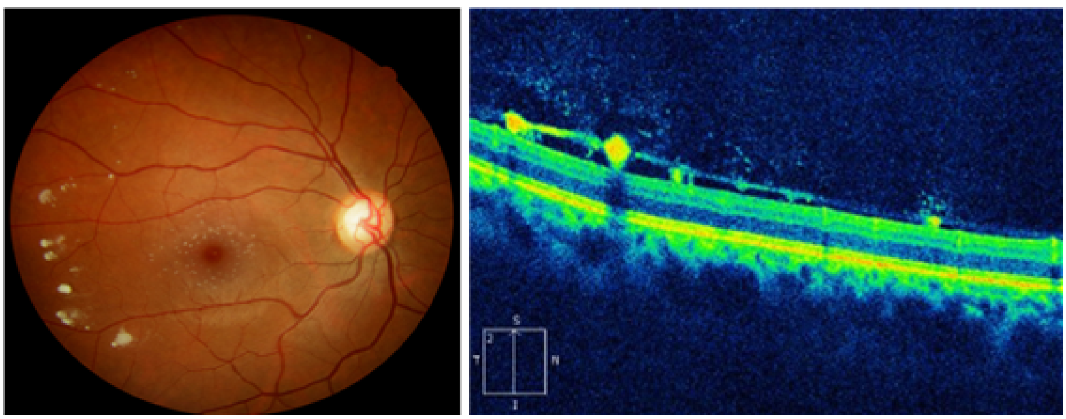


Figure 2. Retinal scan showing lipid deposits in the periphery of the retina and in the perimacular region. The OCT imaging of the peripheral deposits evidenced lesions between the retina and the vitreous.

UVEITIS

Uveitis is another change described in GD. GlcCer accumulation is suggested to be involved in some forms of uveitis. An assessment of the sphingolipids found in the vitreous of a patient with GD showed GlcCer accumulation followed by monocyte and macrophage infiltration[34]. GC have also been found in the choroid of patients with the disease[23].

In one study, 2 (0.4%) of 527 patients with GD1 presented with uveitis. One of them presented with bilateral asymmetric panuveitis with keratic precipitates and vitreitis[35]. Chronic intermediate uveitis with residual snowballs has been reported in patients with GD, with most cases improving with enzyme replacement therapy[36]. Altoon *et al.* reported two cases of patients with uveitis presenting different clinical courses and outcomes. Although one patient showed improvement, chronic uveitis persisted in the older patient, despite undergoing enzyme replacement therapy[35].

It is important to highlight the association between chronic uveitis resistance to clinical treatment and lymphoma (masquerade syndromes). Increased incidence of B-cell and T-cell malignancies, such as multiple myeloma and chronic lymphocytic leukemia, have been reported in patients with GD. Thus, malignancy should be investigated in cases of treatment-resistant chronic uveitis[35].

DECREASED RETINAL NERVE FIBER LAYER (RNFL) THICKNESS

Increased excavation and decreased RNFL, which are suggestive of glaucomatous optic neuropathy, are a rare finding in patients with GD. Some authors attribute the reduction in the nerve fiber layer to the loss of acid β- glucosidase activity, which is associated with oxidative stress and mitochondrial dysfunction[37]. Matos *et al.* described a case of GD3 with suspected glaucoma and markedly decreased RNFL (Figure 3)[31].

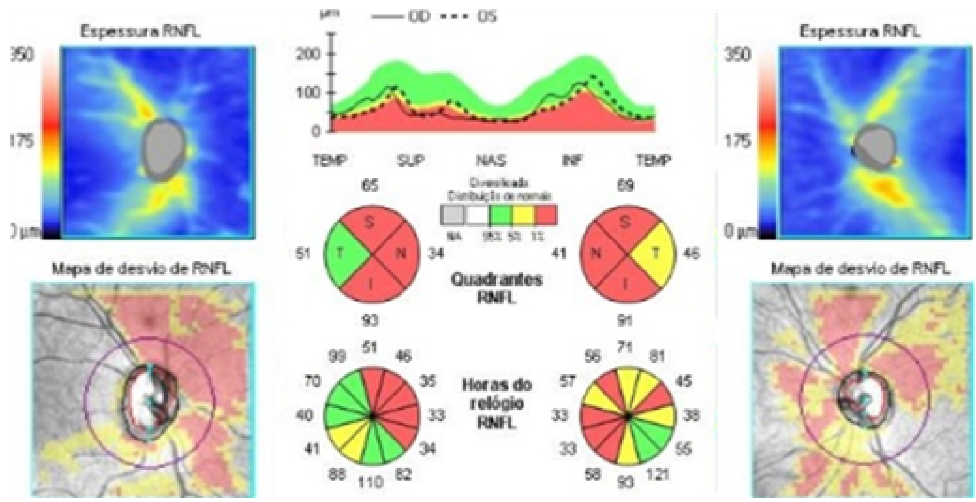


Figure 3. An OCT analysis revealed an intense decrease of the nerve fiber layer in a case of GD3, leading to a suspicion of glaucomatous optic neuropathy.

EYE MOVEMENTS

The detailed examination of eye movements is indispensable in clinical investigation, in addition to being useful in the diagnostic elucidation and classification of GD clinical subtypes in relation to neurological involvement[38].

In the GD2 and GD3 (neuronopathic) clinical forms, the following oculomotor changes have been described: failure or slowing down of horizontal and downward saccadic eye movements, abnormal vestibulo-ocular reflex, and altered optokinetic nystagmus[39,40].

The most frequently occurring oculomotor change in GD3 is early supranuclear motor control dysfunction, which leads to deficient saccadic eye movements, also called “ocular motor apraxia,” “congenital ocular motor apraxia,” “supranuclear gaze palsy,” “gaze palsy,” and “looping”[41]. Children can attempt to compensate deficient saccadic eye movements with head thrusting to move their gaze. In older children, head positioning is often replaced with a kinetic blinking strategy.

The ocular motility deficits noted in some patients can also be associated with an abnormal pulse of innervation to the lateral rectus muscles, which are unable to abduct the eyes due to abducens dysfunction[42]. Children with GD3 presented with limited abduction, ocular motor apraxia, and esotropia. Therefore, GD should be among the diagnostic hypotheses for patients with these signs[43].

Although esotropia can be present in GD, the possibility of it being a consequence of mild abducens palsy cannot be ignored. Hence, it is recommended that patients with GD and esotropia be carefully examined for other eye movement abnormalities before surgery[6,18].

The topography of the lesions that cause abnormal eye movements is uncertain, but the movements are believed to be associated with lesions in several places, including the brain stem, cerebellum, basal ganglia, and neocortex[41].

DIAGNOSIS

GD is diagnosed by assessing the GCase activity in peripheral blood leukocytes, by fibroblast cell culture on the basis of skin biopsy, or by a molecular analysis of mutations. The residual enzyme activity is usually approximately 10%-15% of the normal level[7]. Molecular diagnosis can be performed by GBA gene sequencing. The gene that encodes GCase (GBA1) is located on the long arm of chromosome 1 (1q21) and contains 11 exons. The presence of a highly homologous pseudogene (GBAP) on the same location (16 kb downstream) is responsible for recombination events between GBAP and GBA1 (for example, the Rec-NciI allele)[44].

The diagnosis of ophthalmological manifestations is performed using eye movement and visual acuity assessment, biomicroscopy of the anterior segment, and full fundoscopic examination. Fluorescein angiography[21] and OCT analysis of RNFL[31] can also be used.

TREATMENT

The following two different treatment strategies for GD are currently available: intravenous enzyme replacement therapy (ERT) and orally administered substrate reduction therapy (SRT)[45].

One of the drugs used in ERT is imiglucerase (Cerezyme®, Sanofi- Genzyme, authorized in 1996), produced using Chinese hamster ovary cells. Other recombinant enzymes were developed later: velaglucerase alfa (Vpriv®, Shire, authorized in 2010), produced using human fibroblasts, and taliglucerase alfa (Elelyso®, Pfizer, authorized in 2011), produced using carrot cells.[45]

The aim of the other treatment strategy (SRT) is reducing the production of cellular GlcCer (substrate). Miglustat (Zavesca®, Actelion, authorized in 2002) is a GlcCer synthase inhibitor, reducing GlcCer biosynthesis in GC. Although it can cross the blood-brain barrier, miglustat had no significant effect on the neurological symptoms of patients with GD3.[7] Another substrate inhibitor is eliglustat (Cerdelga®, Sanofi-Genzyme, authorized in 2015), which does not cross the blood–brain barrier and is only indicated for GD1[46].

Treatment for ocular manifestations is controversial and lacks evidence of effectiveness, but eye movement has reportedly shown improvement using miglustat (which reduces the synthesis of GlcCer) after two years of treatment[40]. Posterior segment changes usually do not improve with enzyme replacement medications because of their inability to cross the blood-retinal barrier.[21] A few authors reported visual acuity improvement with vitrectomy and epiretinal membrane peeling in patients with GD3.[25,47]

CONCLUSIONS AND CHALLENGES

Advances in understanding the clinical manifestations of GD are unquestionable; however, the phenotypic heterogeneity of GD for the same gene, the variation in organ involvement, and the complete involvement of macrophages in the pathophysiology of the disease are still to be clarified.

The high cost of GD treatment and the lack of comparative studies of the many treatment strategies challenge researchers. Finding biomarkers that are able to effectively monitor the diagnosis and treatment of GD is one of the aims of several ongoing studies.

Neurological and ophthalmological manifestations are difficult to treat, and drugs capable of effectively controlling these symptoms in patients with GD3 are still being investigated.

Lastly, associations of GD with other diseases are frequently found. In the present review, we present the diversity of ocular findings and highlight the importance of thorough eye examination.

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